REMARKS

Claims 1-28, 30-33, 42, 43, and 46-51 are pending in this application. Claims 2-11, 15, 16, 23-27, 31-33, 42, 43, and 46-51 have been canceled, claims 1, 12-14, 17, 20, 28, 30 have been amended and new claims 52-56 have been added. Accordingly, upon entry of the amendments presented herein, claims 1, 12-14, 17-22, 28, 30, and 52-56 will remain pending in the application.

Support for the amendments to the claims may be found throughout the specification and claims as originally filed. Specifically, support for the amendments to claim 1 may be found at, for example, page 44, lines 1-21, page 8, lines 1-6, and page 20, lines 20-25 of the specification; support for the amendments to claims 12-14 and new claims 52 and 53 may be found at, for example, page 39, lines 1-21, page 40, lines 3-20, page 41, lines 6-21, and page 46, lines 4-32 of the specification; and support for new claims 54-56 may be found at, for example, page 13, lines 2-5 of the specification.

No new matter has been added. Any amendments to and/or cancellation of the claims was done solely to more particularly point out and distinctly claim the subject matter of Applicants' invention in order to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Election / Restriction

Group I (claims 1-22, 42, 43, 46-49, 50, and 51) directed to processes for the enhanced production of pantothenate, comprising culturing a microorganism having a deregulated methylenetetrahydrofolate (MTF) biosynthetic pathway was elected by Applicants with traverse. Applicants gratefully acknowledge the Examiner's indication that the previous Restriction Requirement has been withdrawn and that claims 23-28 and 30-33 will also be examined.

Rejection of Claims 1-28, 30-33, 42, 43, and 46-51 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1-28, 30-33, 42, 43, and 46-51 under 35 U.S.C. § 112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim

the subject matter which applicant regards as the invention" for the recitation of the phrase "pantothenate production is enhanced"

Applicants respectfully submit that amendment of claim 1, and claims dependent therfrom, to recite "such that pantothenate production is enhanced, ***as compared to the production of pantothenate by an unmodified microorganism***" has rendered the Examiner's rejection moot, and accordingly, respectfully request that the foregoing rejection of the claims under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

The Examiner has rejected claims 25-27 under 35 U.S.C. § 112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention".

Applicants respectfully submit that cancellation of claims 25-27 has rendered the Examiner's rejection moot, and accordingly, respectfully request that the foregoing rejection of the claims under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

Rejection of Claims 1-33, 42, 43, and 46-51 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1-33, 42, 43, and 46-51 under 35 U.S.C. §112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Specifically, the Examiner is of the opinion that

> one of skill in the art would not recognize that applicants were in possession of a process for producing pantothenate using a genus of microorganisms having any deregulation of any enzyme/protein in methylenetetrahydrofolate (MTF) biosynthetic pathway (including any GlyA gene product, SerA gene product, and PurR gene product, any deregulation of any enzyme/protein in the pantothenate biosynthetic pathway (including any ketopantoate hydroxymethyltransferase, ketopantoate reductase, pantothenate synthetase, aspartate decarboxylase, pantothenate kinase), any/or deregulation of any enzyme/protein in the isoleucine-valine biosynthetic pathway (including any acetohydroxyacid acid synthetase, acetohydroxyacid isomoreductase, and dihydoxyacid dehydratase.

With respect to claims 2-11, 15, 16, 23-27, 29, 31-32, 42, 43, and 46-51, cancellation of these claims has rendered the Examiner's rejection moot. With respect to claim 1 (from which claims 11-14, 17-22, 28, 30, and 52-55 depend), Applicants respectfully traverse the foregoing rejection on the grounds that there is sufficient written description in Applicants' specification regarding methylenetetrahydrofolate biosynthetic pathway genes and polypeptides, pantothenate biosynthetic pathway genes and polypeptides, and isoleucine valine biosynthetic pathway genes and polypeptides and whether they are up-regulated or down-regulated in order to enhance pantothenate production (discussed in detail below), to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed.

However, in the interest of expediting prosecution and allowance of the pending claims, and in no way acquiescing to the validity of the Examiner's rejection, the claims have been amended to specify the sequence of the biosynthetic pathway gene. Specifically, claim 1, as amended, and claims dependent therefrom, are directed to processes for the enhanced production of pantothenate, comprising ***transforming a Bacillus subtilis cell with a recombinant vector as set forth in SEQ ID NO:28***, selecting a recombinant cell having antibiotic resistance, thereby producing a recombinant microorganism, and culturing said recombinant microorganism under suitable conditions such that pantothenate production is enhanced, as compared to pantothenate production by an unmodified microorganism.

Accordingly, the foregoing rejection has been rendered moot and Applicants respectfully request that this rejection of claims 1-33, 42, 43, and 46-51 under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

Rejection of Claims 1-33, 42, 43, and 46-51 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1-14 and 22-27 under 35 U.S.C. §112, first paragraph because, according to the Examiner,

> the specification, while being enabling for a process for enhanced production of pantothenate using a *B. subtilis* strain tansformed with a plasmid of SEQ ID NOs:24, 25, 28 or 29 which overproduces pantothenate compared to an untransformed *B. subtilis* strain; does not reasonable provide enablement for any other embodiment as recited in the claims.

With respect to claims 2-11, 15, 16, 23-27, 29, 31-32, 42, 43, and 46-51, cancellation of these claims has rendered the Examiner's rejection moot. With respect to claim 1, and claims dependent therefrom, Applicants respectfully traverse the foregoing rejection for the reasons set forth below. As amended, claim 1 is directed to processes for the processes for the enhanced production of pantothenate, comprising ***transforming a Bacillus subtilis cell with a recombinant vector as set forth in SEQ ID NO:28***, selecting a recombinant cell having antibiotic resistance, thereby producing a recombinant microorganism, and culturing said recombinant microorganism under suitable conditions such that pantothenate production is enhanced, as compared to an unmodified microorganism.

Applicants submit that, based on the teachings in Applicants' specification and the knowledge generally available in the art at the time of the invention, one of ordinary skill in the art would be able to make and use the claimed invention using only routine experimentation.

With respect to the scope of the claims and the amount of guidance provided in Applicants' specification, the Examiner is of the opinion that

> [t]he nature and breadth of the claims encompass any process for producing pantothenate using a genus of microorganisms having any deregulation of any enzyme/protein in methylenetetrahydrofolate (MTF) biosynthetic pathway (including any GlyA gene product, SerA gene product, and PurR gene product), any deregulation of any enzyme/protein in the pantothenate biosynthetic pathway (including any ketopantoate hydroxymethyltransferase, ketopantoate reductase, pantothenate synthetase, aspartate decarboxylase, pantothenate kinase), any/or deregulation of any isoleucine-valine biosynthetic pathway (including any acetohydroxyacid acid synthetase, acetohydroxyacid isomeroreductase, and dihydroxyacid dehydratase).
>
> The specification provides guidance and examples for making the following specific *Bacillus subtilis* strains: Example III of the specification discloses a plasmid pAN396 (SEQ ID NO: 24) transformed into a *B. subtilis* strain resulting in the transformed *B. subtilis* producing more pantothenate compared to an untransformed *B. subtilis* strain, where the said plasmid contains a B. subtilis polynucleotide encoding a serine hydroxymethyl transferase (GlyA gene product) obtained using primers of SEQ ID NOs: 22 and 23. Example IV discloses a plasmid pAN393 (SEQ ID NO: 25) transformed into a *B. subtilis* strain resulting in the transformed *B. subtilis* producing more pantothenate compared to an untransformed *B. subtilis* strain, where the said plasmid contains a *B. subtilis* polynucleotide encoding a 3-phosphoglycerate dehydrogenase (SerA gene product) obtained using primers of SEQ ID NOs: 21 and 22. Example VI discloses plasmid pAN838F (SEQ ID NO: 28) transformed

> into a into a *B. subtilis* strain resulting in the transformed *B. subtilis* having a disrupted repressor protein (PurR gene product) and producing more pantothenate compared to an untransformed *B. subtilis* strain, where the said plasmid contains a disrupted *B. subtilis* polynucleotide encoding the repressor protein PurR. Example VII discloses a plasmid pAN395 (SEQ ID NO: 29) transformed into a *B. subtilis* strain resulting in the transformed *B. subtilis* producing more pantothenate compared to an untransformed *B. subtilis* strain, where the said plasmid contains a *B. subtilis* polynucleotide encoding a 3-phosphoglycerate dehydrogenase (SerA gene product) that is expressed from the strong, constitutive promoter.

With respect to the amount of experimentation necessary, the Examiner is of the opinion that

> the specification does not provide guidance, prediction, and working for making any other microorganism to be used in the claimed process for producing pantothenate. Thus, an undue amount of trial and error experimentation must be preformed where such experimentation involves making any microorganism having any deregulation of any enzyme/protein in methylenetetrahydrofolate biosynthetic pathway, any deregulation of any enzyme/protein in the pantothenate biosynthetic pathway, any/or deregulation of any enzyme/protein in the isoleucine-valine biosynthetic pathway; and determining whether the microorganism can overproduce pantothenate compared to an unmodified microorganism. This trial and error experimentation is well outside the scope of routine experimentation. General teaching regarding screening and searching for a specific microorganism that overproduces pantothenate compared to an unmodified microorganism is not guidance for making the claimed invention. In view of the above considerations, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In contrast to the Examiner's assertions, Applicants submit that there are sufficient teachings in Applicants' specification regarding methylenetetrahydrofolate (MTF), pantothenate, and isoleucine-valine biosynthetic pathways, biosynthetic genes, and biosynthetic gene products to enable one of skill in the art to practice the claimed methods without undue experimentation. In particular, Figures 1 and 2 of Applicants' specification schematically teach the pantothenate and isoleucine-valine biosynthetic pathways (Figure 1) and methylenetetrahydrofolate biosynthetic pathway (Figure 2). The biosynthetic enzymes/gene products involved in these

pathways and the corresponding genes encoding the enzymes in these pathways are also indicated in these Figures. Applicants' specification also provides additional teachings with regard to these biosynthetic genes and biosynthetic gene products. Specifically, the specification teaches the function, *i.e.,* enzymatic activities, of pantothenate, MTF, and isoleucine-valine biosynthetic gene products.

Applicants point the Examiner to, for example, page 11, line 37, through page 12, lines 1-8 of the specification which teaches that the methylenetetrahydrofolate (MTF) biosynthetic pathway is the

> biosynthetic pathway involving MTF biosynthetic enzymes (e.g., polypeptides encoded by biosynthetic enzyme-encoding genes), compounds (*e.g.,* substrates, intermediates or products), cofactors and the like utilized in the formation or synthesis of the PanB substrate, MTF. The term "methylenetetrahydrofolate (MTF) biosynthetic pathway" refers to the biosynthetic pathway leading to the synthesis of MTF in vivo (*e.g.,* the pathway in *E. coli*, as depicted in Figure 2) as well as the biosynthetic pathway leading to the synthesis of MTF *in vitro*. The term "methylenetetrahydrofolate (MTF) biosynthetic enzyme" includes any enzyme utilized in the formation of a compound (e.g., intermediate or product) of the methylenetetrahydrofolate (MTF) biosynthetic pathway.

At page 7, lines 32-38, Applicants' specification teaches that the pantothenate biosynthetic pathway is the

> biosynthetic pathway involving pantothenate biosynthetic enzymes (*e.g.*, polypeptides encoded by biosynthetic enzyme-encoding genes), compounds (*e.g.*, substrates, intermediates or products), cofactors and the like utilized in the formation or synthesis of pantothenate. The term "pantothenate biosynthetic pathway" includes the biosynthetic pathway leading to the synthesis of pantothenate in microorganisms (*e.g.*, *in vivo*) as well as the biosynthetic pathway leading to the synthesis of pantothenate *in vitro*.

And at page 8, line 30, through page 9, lines 1-3, Applicants' specification teaches that a pantothenate biosynthetic enzyme

> includes any enzyme utilized in the formation of a compound (*e.g.*, intermediate or product) of the pantothenate biosynthetic pathway. For example, synthesis of pantoate from α-ketoisovalerate (α-KIV) proceeds *via* the intermediate, ketopantoate. Formation of ketopantoate is catalyzed by the pantothenate biosynthetic enzyme PanB or ketopantoate

> hydroxymethyltransferase (the *panB* gene product). Formation of pantoate is catalyzed by the pantothenate biosynthetic enzyme PanE1 or ketopantoate reductase (the *panE1* gene product). Synthesis of β-alanine from aspartate is catalyzed by the pantothenate biosynthetic enzyme PanD or aspartate-α-decarboxylase (the *panD* gene product). Formation of pantothenate from pantoate and β-alanine (*e.g.*, condensation) is catalyzed by the pantothenate biosynthetic enzyme PanC or pantothenate synthetase (the *panC* gene product).

Applicants' specification also teaches that the isoleucine-valine biosynthetic pathway is

> the biosynthetic pathway involving isoleucine-valine biosynthetic enzymes (*e.g.*, polypeptides encoded by biosynthetic enzyme-encoding genes), compounds (*e.g.*, substrates, intermediates or products), cofactors and the like utilized in the formation or synthesis of conversion of pyruvate to valine or isoleucine. The term "isoleucine-valine biosynthetic pathway" includes the biosynthetic pathway leading to the synthesis of valine or isoleucine in microorganisms (*e.g., in vivo*) as well as the biosynthetic pathway leading to the synthesis of valine or isoleucine *in vitro*. (see, page 9, lines 30-36 of the specification).

At page 10, lines 8-21, Applicants' specification teaches that a isoleucine-valine biosynthetic enzyme

> includes any enzyme utilized in the formation of a compound (e.g., intermediate or product) of the isoleucine-valine biosynthetic pathway. According to Figure 1, synthesis of valine from pyruvate proceeds via the intermediates, acetolactate, α,β-dihydroxyisovalerate (α,β-DHIV) and α-ketoisovalerate (α-KIV). Formation of acetolactate from pyruvate is catalyzed by the isoleucine-valine biosynthetic enzyme acetohydroxyacid synthetase (the *ilvBN* gene products, or alternatively, the *alsS* gene product). Formation of α,β-DHIV from acetolactate is catalyzed by the isoleucine-valine biosynthetic enzyme acetohydroxyacid isomeroreductase (the *ilvC* gene product). Synthesis of α-KIV from α,β-DHIV is catalyzed by the isoleucine-valine biosynthetic enzyme dihydroxyacid dehydratase (the *ilvD* gene product). Moreover, valine and isoleucine can be interconverted with their respective α-keto compounds by branched chain amino acid transaminases. Isoleucine-valine biosynthetic enzymes may also perform an alternative function as enzymes in the HMBPA biosynthetic pathway described herein.

The instant specification further provides teachings regarding methods to target biosynthetic genes encoding MTF, pantothenate, and isoleucine-valine biosynthetic enzymes (see, *e.g.,* pages 13-18 of the specification), recombinant nucleic acid molecules and vectors for use in the methods of the invention (see, *e.g.,* pages 18-22 of the specification), as well as recombinant microorganisms, methods of culturing these microorganisms (see, *e.g.,* pages 22-31 of the specification), and methods of assaying for pantothenate production (see, *e.g.,* Example I-IX at pages 30-51 of the specification).

Furthermore, Applicants have provided working examples of methods to target biosynthetic genes, methods of generating recombinant vectors, and methods of culturing recombinant microorganisms in order to enhance pantothenate production. More specifically, Example I (at page 32 of the specification) teaches the construction of several recombinant vectors and microorganisms with overexpressed *pan*BCD, and *pan*E1 genes as well as overexpressed of *ilv*D, and *ilv*BNC and the enhancement of pantothenate production in these microorganisms; Examples III, IV, and V (at page 38, page 40, page 41, respectively, of the specification) teach the construction of recombinant vectors and microorganisms in which the *gly*A and/or *ser*A genes are overexpressed and pantothenate production is enhanced; and Example VI (at pages 43) teach the construction of recombinant vectors and microorganisms in which the chromosomal *purR* gene is disrupted and pantothenate production is enhanced.

In addition to the teachings in Applicants' specification, Applicants submit that methods to generate recombinant vectors and recombinant microorganisms with deregulated biosynthetic genes are commonly known and routine to one of skill in the art (see, *e.g.,* the references cited on Form SB-08 submitted herewith along with a Supplemental Information Disclosure Statement).

Moreover, Applicants submit that the invention must be given the presumption of correctness and operativeness. As set forth in *In re Marzocchi*, 439 F.2d 220,

> [a]s a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112.

Accordingly, Applicants submit that that based on the teachings and guidelines of the present invention as disclosed in the application, in combination with the knowledge of one of skill in the art at the time the application was filed, processes for the processes for the enhanced production of pantothenate, comprising ***culturing a microorganism having a deregulated MTF, pantothenate, and/or isoleucine-valine biosynthetic*** pathway, under conditions such that pantothenate production is enhanced, are routine to one skilled in the art.

In view of the ample guidance provided in the specification and the references cited therein, and the extensive knowledge available in the art, the instant specification enables a person of ordinary skill in the art to make and use the claimed methods without undue experimentation.

As stated in *Forman*, "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance." *Ex parte Forman*, 230 USPQ 546, 547 (Bd. App. 1986). As also pointed out by the Federal Circuit in *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ 2d 1321 (1990), "[i]t is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification." 15 USPQ 2d at 1329. See, also *In re Brana*, 34 USPQ 2d 1436 (Fed. Cir. 1995).

Nevertheless, in the interest of expediting prosecution and allowance of the pending claims, and in no way acquiescing to the validity of the Examiner's rejection, the claims have been amended to specify the sequence of the biosynthetic pathway gene. Specifically, claim 1, as amended, and claims dependent therefrom, are directed to processes for the enhanced production of pantothenate, comprising ***transforming a Bacillus subtilis cell with a recombinant vector as set forth in SEQ ID NO:28***, selecting a recombinant cell having antibiotic resistance, thereby producing a recombinant microorganism, and culturing said recombinant microorganism under suitable conditions such that pantothenate production is enhanced, as compared to pantothenate production in an unmodified microorganism.

Accordingly, Applicants respectfully request that the foregoing rejection of the claims under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

SUMMARY

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call the undersigned at (617) 227-7400.

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Respectfully submitted,

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